

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

by fax and post Bird

To:

PEDIGO, Paul F.  
ALSTON & BIRD LLP  
Bank of America Plaza  
101 South Tryon Street  
Suite 4000  
Charlotte, NC 28234-4009  
ETATS-UNIS D'AMERIQUE

FAX: 704 334 2014

PCT FEB 22 2002

Received By  
NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year)

13.02.2002

Applicant's or agent's file reference

4848-37-1

204836

**IMPORTANT NOTIFICATION**

International application No.  
PCT/US00/41070

International filing date (day/month/year)  
04/10/2000

Priority date (day/month/year)  
04/10/1999

Applicant

SHEARWATER POLYMERS, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

**4. REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Cleere, C

Tel. +49 89 2399-7713



## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)


Applicant's or agent's file reference 4848-37-1	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/41070	International filing date (day/month/year) 04/10/2000	Priority date (day/month/year) 04/10/1999
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant SHEARWATER POLYMERS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  01/05/2001	Date of completion of this report  13.02.2002
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Vogt, T  Telephone No. +49 89 2399 8477



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/41070

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-23 as originally filed

**Claims, No.:**

1-29 as originally filed

**Drawings, sheets:**

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/41070

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**II. Priority**

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1, 16-18, 22-28 and 17-29.

because:

☒ the said international application, or the said claims Nos. 17-29 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/41070

could be formed.

- ☒ no international search report has been established for the said claims Nos. 1, 16-18, 22-28.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 5, 6, 11, 12, 15, 19-21
	No:	Claims 2-4, 7-10, 13, 14
Inventive step (IS)	Yes:	Claims
	No:	Claims 2-15, 19-21, 29
Industrial applicability (IA)	Yes:	Claims 2-15
	No:	Claims

**2. Citations and explanations  
see separate sheet**

**II Priority.**

The present application validly claims priority of the filing date of US-applications 60/166589 (19.11.1999) and 60/157503 (04.10.1999).

**III No opinion.**

Claims 17-29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**V Reasoned Statement.**

Subject matter of the present application.

The provision of conjugates comprising a peptide and a water soluble non-peptidic polymer.

Cited prior art documents (Rule 64(1) PCT).

- D1: WITT ET AL. (08.2001) J. PHARM. EXP. THERAPEUT., AM. SOC. PHARM. 298, 848-856.  
D2: WO 95 00162 A  
D3: WO 91 16929 A  
D4: US-A-5 932 462  
D5: US-A-5 681 811

D1 does not form part of prior art under Rule 64(1) or (3) PCT.

Novelty (Art. 33(2) PCT).

D2 relates to conjugates of peptides with non-antigenic polymers (eg. PEG, cf. claims). D2 states that this modification results in a longer lifetime. The problem solved by D2 is to control the number and location of polymers attached to a peptide, to make sure that the bioactivity of these peptides is not hampered by steric hindrance of the covalently attached polymer (cf. p. 2). D2 solves this problem by making sure that the polymer can only attach to one of the termini of the peptide. Peptides suitable for the invention of D2 are: dynorphin A, neo-endorphins, and opioid peptides (p. 7, l. 28-30). In example 6 of

D2, dynorphin A and two endorphin derivatives are conjugated to PEG-5K. Hence, D2 is prejudicial to the novelty of the subject matter of claims 2, 4, 7-10, 13, 14 and 16.

D3 does not appear to contain information relevant to the present application.

D4 discloses multi-armed mono functional PEG for conjugation to proteins to increase the life span thereof (cf. claims). D4 mentions that thousands of proteins and enzymes can be modified with the multi-armed mono functional PEG and mentions dynorphin in particular (col. 36, l. 42).

Hence, D4 is prejudicial to the novelty of the subject matter of claims 2 and 8-10.

D5 discloses conjugates of bioactive agents with a non-peptidic polymer characterised in that the polymer comprises a hydrophilic and a lipophilic moiety (cf. claims). D5 anticipates endorphins, enkephalins (cf. claims 37-47).

Hence, D5 is prejudicial against the novelty of the subject matter of claims 2 and 3.

It is noted that although no search report was established for claim 1, said claim lacks novelty over D2, D4 and D5.

To summarize: the subject matter of claims 5, 6 11, 12, 15 and 19-21 are novel over the cited prior art, because biphalin, DPDPE, the dimeric form of the peptide of claim 3, modification with PEG-2000, and the blood brain barrier are not mentioned in the cited prior art.

Inventive step (Art. 33(3) PCT).

Since claims 2-4, 7-10, 13 and 14 lack novelty they also lack an inventive step.

D2 anticipates 'opioid peptides' for use in its invention. The peptides of claims 3, 5 and 6 all belong to this group, and are therefore anticipated by D2. Hence, claims 5 and 6 lack an inventive step over D2.

The optimum size of the polymer and the number of polymers per opioid (claims 11-15) is considered to be a matter of standard laboratory experimentation, and is the result of two mechanisms: 1) life time (increases with increasing Mw), and 2) transport rate

across the BBB (decreases with increasing Mw). Claims 11-15 therefore also lacks an inventive step over D2 and D5.

Claims 17-26 are construed to read 'The conjugate of claim 1 for use as a medicament, the use of the conjugate of claim 1 for preparing a medicament'. These claims are only patentable with a patentable compound claim since the use of such conjugates appears to be anticipated by D2 and D5.

The conjugate of claim 29 differs from the conjugate of claim 1 in that it comprises a bi-functional polymer. It does not meet the requirement of inventive step over standard drug targeting strategies using conjugates of a ligand (eg. growth factors) and a bioactive compound (eg. marker, drug, etc.) (cf. WO-A-00/07543 for a recent publication).

Industrial applicability (Art. 33(4) PCT).

For the assessment of the present claims 17-29 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.